REMARKS

I. Status of the Application

Claims 1-23 were filed in the original application. In the Response to the Restriction Requirement mailed June 13, 2006, claims 1-12 were cancelled. In the Amendment and Response to the Office Action of May 3, 2007, claims 15-19, 22, and 23 were cancelled, and claims 13, 14, 20 and 21 were amended. In the Amendment and Response to Final Office Action of December 31, 2007 claims 13 and 14 were amended and claim 27 was added. In the Amendment and Response to Office Action of April 11, 2008, claim 13 was amended, and claim 28 was added. In the present Amendment and Response to the Office Action of February 4, 2009, claim 13 is amended. Applicants note that all amendments of claims are made without acquiescing to any of the Examiner's arguments or rejections, and solely for the purpose of expediting the patent application process in a manner consistent with the PTO's Patent Business Goals (PBG),[1] and without waiving the right to prosecute the amended or cancelled claims (or similar claims) in the future.

In the present Amendment and Response to the Office Action of February 4, 2008 claim 13 is amended. Support for amended claim 13 may be found throughout the Specification at, for example, page 69, lines 29-30, page 70, lines 23-25, and page 79, lines 16-17.

Thus, claims 13, 14, 20, 21 and 24-28 are currently pending in the application.

II. Claim Rejection

In the Office Action of February 4, 2009 there is one rejection. The currently pending rejection is:

1 65 Fed. Reg. 54603 (Sept. 8, 2000).

1. Claims 13-14, 20-21, and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement

1. Claims 13-14, 20-21 and 24-26 are Enabled

In the Office Action of February 4, 2009 the Office notes:

"The ability to reasonably predict the capacity of a single bacterial immunogen to induce protective immunity from *in vitro* antibody reactivity studies is problematic. Unfortunately, the art is replete with instances where even well characterized antigens that induce an *in vitro* neutralizing antibody response fail to elicit *in vivo* protective immunity. See Blasi et al. (Clinical Pulmonary Medicine, 2002, 9/1, 6-12-Abstract) wherein *in vitro* data regarding C. pneumonia activity/treatment could not predict optimal dosing and length for in vivo activity/treatment. Accordingly, the art indicates that it would require undue experimentation to formulate and use a successful anti-*vimentin antibody* agent without prior demonstration of efficacy in the particular diseases." (Office Action of February 4, 1009, page 7.)

Applicants note that claim 13 does not recite administration of a bacterial immunogen, administration of an antigen, induction of a neutralizing antibody response, or administration of antibiotic. Moreover, Applicants note that Blasi does not recite, teach or suggest vimentin or anti-vimentin specific antibodies. Instead, Blasi addresses optimal dosing and length of antibiotic treatment (*i.e.*, small molecular compound) for *Chlamydia pneumonia*. Accordingly, the Office's citation of the Blasi reference fails to indicate that it would require undue experimentation to formulate and use a successful anti-vimentin antibody agent.

In view of the above, the Applicants request that this rejection be withdrawn.

In the Office Action of February 4, 2009 the Office notes:

"The prior art teaches that the presence of anti vimentin antibodies is linked to detrimental results in patients. For example, the reference to Yang et al. (Clinical and Experimental Immunology, April 2002, Vol 128, No. 1, pp 169-174) were high levels of antivimentin antibodies are linked to IPF (idiopathic pulmonary fibrosis), NSIP (non-specific interstitial pneumonia), systemic lupus erythematosus, progressive vascular sclerosis and RA. Thus from the prior art teaching the administration of anti-vimentin antibodies to a subject would appear to induce diseases and/or disorders linked to bacterial pathogens. This is contrary to the instant invention which is directed to reduced risk of mortality. See abstract and page 128 – Discussion." (Office Action of February 4, 2009, page 4.)

And

"Specifically, anti-*vimentin antibodies* do not necessarily end up providing any protective immunoprotection and have actually been linked to various disease states. Yang et al. (Clinical and Experimental Immunology, April 2002, Vol. 128, No. 1, pp 169-174.)

Applicants respectfully disagree with the Office's assertions. First, and contrary to the Office's assertions, in vivo Experimental Example 7 clearly demonstrates that anti-vimentin antibodies protect against infection with lethal doses of bacteria.

In view of the above, the Applicants request that this rejection be withdrawn.

Second, claim 13 does not address mortality from diseases and disorders that are not associated with a pathogen. Contrary to the Office's interpretation of Yang, none of the diseases and disorders cited in Yang (*i.e.,* IPF (idiopathic pulmonary fibrosis), NSIP (non-specific interstitial pneumonia), systemic lupus erythematosus, progressive vascular sclerosis and RA) are linked to bacterial pathogens. Nor does Yang, or the Office, demonstrate that the diseases and disorders recited by Yang are caused by administration of an anti-vimentin antibody.

In view of the above, Applicants request that this rejection be withdrawn.

Moreover, even if Yang was properly cited in a 112 rejection (Applicants believe it is not), Yang does not teach or suggest administration of an anti-vimentin antibody. Yang's antibodies "are formed in some patients with IPF, idiopathic NSIP and NSIP associated with polymyositis/dermatomyositis" (Yang, page 173). Thus, Yang is not on point as the detrimental effect observed was related to specific patient types under specific conditions. Nor can Yang be reasonably extended to make the point raised by the Office. These facts were included in the Amendment and Response to Final Office Action of December 31, 2007, and in the Amendment and Response to the Office Action of April 11, 2008, and were not addressed in the Office Action of February 4, 2009.

In view of the above, the Applicants request that this rejection be withdrawn.

In turn, even if there were "various disease states" attendant to administration of anti-vimentin antibody (Applicants believe that the Office has provided no valid evidence in support of such an argument), the presence or absence of side effects does not support rejection under 35 U.S.C. 112, first paragraph. The Office provides no evidence that administration of anti-vimentin antibody to reduce mortality in pathogen-infected subjects has deleterious side effects, or that such methods would find no use even if there were deleterious side effects. To the contrary, the Specification shows a clear benefit. Thus, the evidence of record does not support the rejection. These facts were included in the Amendment and Response to Final Office Action of December 31, 2007, and in the Amendment and Response to the Office Action of April 11, 2008, and were not addressed in the Office Action of February 4, 2009.

In view of the above, the Applicants request that this rejection be withdrawn.

In the Office Action of February 4, 2009 the Office argues:

> "The prior art teaches that species specific antibodies against vimentin have different reactivity. See abstract to Bohn et al. (Experimental Cell Research, Vol 201., No. 1, July, 1992, pages 1-7). The prior art also teaches that in vitro results can not predict in vivo antibody responses. See Pallini et al. (Journal of Neuro-

Oncology, Vol. 49, 2000, pages 9-17)." (Office Action of February 4, 2009, page 5.)

The Applicants respectfully disagree with the relevance of the Office's assertions. As the Examiner acknowledges, Experimental Examples 6 and 7 of the Specification provide explicit and clear cut *in vivo* data. Example 6 shows that a decrement in vimentin prolongs life after injections of lethal doses of *E. coli*. Example 7 shows that specific intervention with anti-vimentin antibody reduces mortality after injections of lethal doses of *E. coli*.

To the contrary, Pallini describes the behavior of brain cancer cells *in vitro*. Pallini does not teach, suggest, or even consider *in vitro* or *in vivo* consequences of anti-vimentin antibody administration on a pathogen, or on a subject having a pathogen. Bohn describes anti-vimentin antibody reaction patterns on vertebrate cells. Bohn does not teach, suggest, or even consider *in vitro* or *in vivo* consequences of anti-vimentin antibody administration on a pathogen, or on a subject having a pathogen. Accordingly, nothing in Pallini or Bohn is relevant to whether or not one skilled in the art would be enabled to make and/or use the inventions of the present claims. These facts were included in the Amendment and Response to Final Office Action of December 31, 2007, and in the Amendment and Response to the Office Action of April 11, 2008, and were not addressed in the Office Action of February 4, 2009.

In view of the above, the Applicants request that this rejection be withdrawn.

In the Office Action of February 4, 2009 the Office argues:

"The anti-vimentin antibody art is highly unpredictable and the instant specification fails to provide any information that anti-vimentin antibodies would protection (reduce mortality) in a human with a pathogen." (Office Action of February 4, 2009, page 5.)

Applicants respectfully disagree with the Office's assertions.

First, in the Office Action of Feburary 4, 2009 the Office fails to provide any evidence that "the anti-vimentin antibody art is highly unpredictable", other than the Office's own conclusory speculations.

In view of the above, the Applicants request that this rejection be withdrawn.

Second, in the Office Action of February 4, 2009 the Office fails to provide any evidence that murine models of bacterial infection and sepsis fail to correspond to bacterial infection and sepsis in other species, for example, humans.

In view of the above, the Applicants request that this rejection be withdrawn.

Third, in the Office Action of February 4, 2009 the Office fails to cite to the statute, code, MPEP, case law or other authority in support of its argument that embodiments of claims in humans and other species are not enabled by the disclosure of corresponding experimental results in small animals. Animal models are routinely used to assess the efficacy of treatment prior to the treatment of humans. The Patent Office routinely accepts such animal data as proof of concept since experiments on humans require regulatory approval. Only where the patent office can show that an animal model is unreliable is the Office's burden met in issuing a proper rejection.

In view of the above, the Applicants request that this rejection be withdrawn.

In the Office Action of February 4, 2009 the Office argues:

> "The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims." (Office Action of Feburary 4, 2009, page 3.)

Applicants respectfully disagree with the Office's assertion. As noted by Kontny *et al.* (Kontny, E., Kurowska, M., Szczepanska, K. & Maslinski, W. Rottlerin, a PKC isozyme-selective inhibitor, affects signaling events and cytokine production in human monocytes. *J Leukoc Biol* **67**, 249-58. (2000), incorporated by reference in the Specification at page 79, line 23), (hereinafter "Kontny"):

> "Monocytes play a critical role in inflammation by releasing oxygen metabolites, lysosomal enzymes, arachidonic acid metabolites, and pro-inflammatory

cytokines, such as tumor necrosis factor a (TNF-a) and interleukins (IL-1, IL-6, IL-8). Pro-inflammatory cytokines play a crucial role in the immune response, hematopoiesis, and inflammation." (Kontny, page 249, col. 1, lines 1-6.)

And:

"The monocyte-activating agents that induce the production of pro-inflammatory cytokines include: LPS, a surface component of gram-negative bacteria released on host infection, the antigen-antibody complexes and cytokines formed during immune response, as well as phorbol esters [the activators of classical and novel isoenzymes of the protein kinase C (PKC) family], used in *in vitro* studies." (Kontny, page 249, col. 1, line 15 – col. 2, line 4.) (Emphasis added.)

Thus, the cytokine TNF-a is released from monocytes upon infection by bacteria. In turn:

"Experiments conducted during the development of the present invention also show that the anti-inflammatory cytokine Interleukin-10 (IL-10), which has been found to exert its effect on macrophages by inhibiting the PKC pathway, blocks vimentin secretion. In addition, the pro-inflammatory cytokine tumor necrosis factor-alpha triggers vimentin secretion that cannot be blocked by the PKC blocker GÖ6983. A role for individual PKC isoenzymes in the induction of pro-inflammatory cytokine synthesis, including that of TNF-α has been identified (35). IL-10 potently suppresses many effector functions of monocytes and macrophages, including the release of cytokines such as TNF-α [27]. Thus, an amplification cascade in which stimulation of the PKC pathway triggers secretion of vimentin as well as production of TNF-α, which then activates others pathways leading to vimentin secretion is initiated." (Specification, page 8, lines 3-13.) (Emphasis added.)

And:

"The anti-inflammatory cytokine IL-10, a potent inhibitor of activated macrophages, exerts its effect by inhibiting the PKC pathway [25,26]. Consistent with these findings, IL-10 markedly decreased the secretion of vimentin as shown by Western blot of the supernatants of 12 day MDM (Figure 5a). Since this physiological anti-inflammatory signal blocks vimentin secretion, we asked whether known pro-inflammatory stimulators could enhance this process. TNF-α is a well-characterized cytokine that is known to act in opposition to IL-10 in macrophages [27]. In Figures 5b and 5c we show that very low doses of TNF-α can induce the secretion of vimentin up to 120 fold by 1 day human monocytes maintained in 10% human serum. In currently accepted models of the TNF-α pathway, signaling does not occur through PKC. Consistent with this theory, the secretion of vimentin from 40% treated MDM was not blocked by GÖ6983 in the presence of TNF-α. Thus, both the PKC and TNF-α activation pathways mediate the secretion of vimentin by MDM." (Specification , page 77, lines 1-14.) (Emphasis added.)

Accordingly, Applicants respectfully submit that the Specification enables the skilled artisan to recognize that infection and sepsis with a pathogen giving rise to pro-inflammatory cytokines that trigger vimentin secretion predictably benefit by treatment with anti-viementin antibodies. In turn, the Specification provides explicit support for the methods of reducing mortality in a subject having a pathogen of the presently claimed invention *i.e.*, administration of anti-vimentin antibodies. Morevoer, one skilled in the art finds abundant details for the methods of use of the anti-vimentin antibodies of the presently claimed invention throughout the Specification at, for example, "**II. Secretory Vimentin Antibodies**" line 1, page 37 to line 5 page 40, and "**V. Secretory Vimentin Pharmaceutical Compositions**" line 16, page 63 to line 2, page 68. These facts were included in the Amendment and Response to Final Office Action of December 31, 2007, and in the Amendment and Response to Office Action of April 11, 2008, but were not addressed in the Office Action of February 4, 2009. However, in order to expedite the

prosecution of the present application, without acquiescing to the Office's rejection, and while reserving the right to prosecute the original claims in the future, Applicants have amended claim 13 to recite "an anti-vimentin antibody that binds to vimentin and inhibits vimentin activity".

In view of the above, the Applicants request that this rejection be withdrawn.

CONCLUSION

All grounds of rejection of the Final Office Action dated February 4, 2009 have been addressed, and reconsideration of the application is respectfully requested. It is respectfully submitted that the Applicant's claims should be passed into allowance. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourage the Examiner to call the undersigned collect at (608) 218-6900.

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